CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209449Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 25, 2017
From	Lisa Soule, M.D., Acting Associate Director, Division of Gastroenterology and Inborn Errors Products
Subject	Division Director Summary Review
NDA/BLA #	NDA 209-449
Applicant Name	Cycle Pharmaceuticals, Ltd.
Date of Submission	September 26, 2016
PDUFA Goal Date	July 26, 2017
Proprietary Name / Established (USAN) Name	Nityr nitisinone
Dosage Forms / Strength	Oral tablet, 2, 5 and 10 mg, (0.5-1 mg/kg twice daily)
Proposed Indication(s)	Treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Patroula Smpokou, M.D.
Pharmacology Toxicology Review	Fresnida Ramos, Ph.D./David Joseph, Ph.D.
CMC Review/OBP Review	Hitesh Shroff, Ph.D. (application technical lead), Hong Cai, Ph.D./Moo-Jhong Rhee, Ph.D. (drug product & environmental analysis), Tianhong Tim Zhou, Ph.D. (process and microbiology), Peng Duan, Ph.D./Tien Mien Chen, Ph.D. (biopharmaceutics), Oumou Barry (regulatory business process manager), Paul Perdue, Jr. (ORA lead)
Clinical Pharmacology Review	Shen Li, Ph.D., Insook Kim, Ph.D.
OPDP	Meeta Patel, Pharm.D.
OSI	Srinivas Chennamaneni, Ph.D./Charles Bonapace, Pharm.D., and Shila Nkah, OSIS
CDTL Review	Joette Meyer, Pharm.D.
OSE/DMEPA	Sherly Abraham, R.Ph., Sarah Vee, Pharm.D.
Other: Division of Pediatric and Maternal Health	Melanie Bhatnagar, M.D./Mona Khurana, M.D./John Alexander, M.D., M.P.H. (pediatrics) Tamara Johnson, M.D., M.S./Lynne Yao, M.D. (maternal health)
Other: Division of Medical Policy Programs, Patient Labeling Team	Karen Dowdy, RN, BSN/Marcia Williams Ph.D./ LaShawn Griffiths, MSHS-PH, BSN, RN

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

The Applicant submitted an NDA under Section 505(b)(2) of the Food, Drug, and Cosmetic Act for room temperature-stable immediate-release nitisinone tablets for the indication of "treatment of patients with hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine." There is an approved oral capsule formulation marketed as Orfadin capsules (approved in 2002 under NDA 21-232), which is to be stored refrigerated (or, since approval of a chemistry, manufacturing and controls [CMC] supplement in February 2017, may be stored for up to 45 days at room temperature). The current application is based on demonstration of bioequivalence to the listed drug, Orfadin, to permit reliance on the Agency's findings of safety and efficacy for Orfadin.

The tablet formulation contains the same active pharmaceutical ingredient with some differences in excipients compared to the capsule formulation. Orfadin is currently marketed in the US, the European Union and Australia. The current Applicant's tablet formulation was approved in Canada in November, 2016, and (b) (4)

As for the listed drug Orfadin, dosing is started at 0.5 mg/kg given orally twice daily, and is titrated according to laboratory or clinical response to a maximum dose of 1 mg/kg administered orally twice daily. Orfadin was also approved as an oral suspension under NDA 206-356 in 2016. Dosing instructions are provided for patients who cannot swallow capsules and who are intolerant to the oral suspension to allow for opening the capsules and suspending the contents in water, formula, or applesauce. Orfadin is labeled to be taken at least one hour before or two hours after a meal.

In addition to tablet administration, the Applicant has proposed to provide for use of the drug by patients who cannot swallow tablets. This will be accomplished by including in labeling instructions for administering the product either as 1) crushed tablets mixed with applesauce, or 2) a suspension of disintegrated tablets in water in a 5 ml oral syringe.

The review of this application was conducted as a Standard review.

2. Background

HT-1 results from an autosomal recessive gene mutation resulting in a deficiency of fumarylacetoacetate hydrolase (FAH). Disruption of the tyrosine catabolic pathway leads to accumulation of toxic intermediates and metabolites, which results in significant hepatic, renal and neurological pathology. HT-1 has a birth incidence of about 1 per 100,000 persons, and typically presents in infancy. Elevated urinary succinylacetone is pathognomic of HT-1, and this assessment, along with other biochemical parameters, is also used to evaluate the treatment effect and titrate the dose of nitisinone.

Current management of HT-1 consists of restriction of dietary tyrosine and phenylalanine, along with treatment with nitisinone, which inhibits degradation of tyrosine via inhibition of 4-hydroxyphenylpyruvate dioxygenase, an enzyme upstream of FAH, preventing the accumulation of the toxic intermediates. Lifelong treatment with nitisinone is necessary, along with dietary restrictions.

The tablet formulation of nitisinone was developed under IND 121,021. The Division held a PreIND meeting with the Applicant in March 2014 to discuss CMC issues relating to the development of a room temperature-stable tablet formulation, and the acceptability of a biowaiver request based on *in vitro* dissolution comparisons to Orfadin. The Division advised that a biowaiver would not be granted because an *in vivo* bioequivalence (BE) study is required to support a different dosage form; however, a waiver request for the lower strength tablets might be acceptable if bioequivalence of the higher strength tablet were demonstrated. The Division also recommended conduct of a food effect study. An advice meeting was held in June 2015 for further discussion of these topics.

The Applicant requested orphan drug designation on August 2, 2016. This request was denied by the Office of Orphan Drug Products (OODP) on December 13, 2016. Denial was based on 21 CFR 316.20(a), which states that the sponsor of a drug that is otherwise the same as an approved drug must "present a plausible hypothesis that its drug may be clinically superior to the first drug." Although the Applicant claimed superiority on the basis of stability at room temperature, evidence that there is no food effect for this product, and smaller size of the tablets compared to Orfadin capsules, OOPD noted that the clinical superiority claim was based only on comparison to Orfadin capsules, while clinical superiority to all approved formulations (i.e., to the Orfadin suspension as well) is needed to support orphan drug designation. OOPD determined that the Applicant's claims provided evidence of increased convenience, but did not provide a plausible hypothesis of clinical superiority.

3. CMC/Device

I concur with the OPQ recommendation for approval. The following conclusions were made by the OPQ review team:

- Sufficient information is provided to ensure consistent manufacturing of the drug substance with regard to identity, strength, purity and quality.
- The Applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.
- Based on stability testing, an expiry of 24 months when stored at room temperature in the proposed container closure system is granted.
- The claim for the Categorical Exclusion for the Environmental Assessment is granted.
- The Office of Process and Facilities has made a final overall "Approval" recommendation for the facilities involved in this application.
- The CMC sections of the revised labeling were found acceptable.

As the bioavailability/bioequivalence (BA/BE) study was conducted using only the proposed 10 mg tablets, the Applicant requested a biowaiver for the 2 mg and 5 mg tablets. This was acceptable to the Biopharmaceutics team based on the comparative dissolution profile data for the two lower strengths and the 10 mg strength. The dissolution method and acceptance criteria were also found acceptable.

The Applicant supported the administration of 1) crushed tablets in applesauce or 2) tablets dissolved into a suspension in water, given by oral syringe, on the basis of dose recovery results. (b) (4)

[redacted] The Applicant has agreed to label the product for use within two hours after preparation, and to a post-marketing commitment to conduct an assay to assure the strength of the product during the use period and provide the results within two months after approval (by September 26, 2017; see Section 13). This is acceptable to the CMC and Microbiology reviewers.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

The Applicant submitted a single nonclinical study, a computational toxicology assessment, to assess mutagenicity risk of potential impurities in accord with ICH M7. Upon review, it was determined that the potential impurities should be considered non-mutagenic; however, the acceptance criterion for total impurities in the drug product was lowered to ≤ [redacted]% vs. the ≤ [redacted]% originally proposed by the Applicant.

Labeling of Sections 8.1, 8.2, and 13 was found to be acceptable.

5. Clinical Pharmacology

I concur with the clinical pharmacology review team's conclusion that the application is acceptable provided agreement on labeling is reached (see Section 12).

The Applicant conducted three clinical pharmacology studies in healthy volunteers to support this 505(b)(2) application:

- Study CT-001, which evaluated the effect of a change in the proportion of an excipient (glyceryl dibehenate [redacted]) on bioequivalence to the approved drug Orfadin (higher [redacted] content was included in an intermediate formulation)
- Study CT-002, which evaluated the food effect of the proposed product
- Study CT-003, which was the relative BA/BE study relied upon to bridge the proposed product to Orfadin

The results of Study CT-003, which was conducted using the 10 mg tablet/capsule under fasted conditions, supported the bridging of the to-be-marketed product to Orfadin, and are shown in Table 1. The statistical criteria applied to demonstration of bioequivalence were met. Exposure was defined as area under the curve based on PK samples collected over 120 hours ($AUC_{0\text{-}120\ hr}$) because of the long half-life (54 hours) of nitisinone. The calibration standard curve for nitisinone concentrations was determined to be representative of the study sample concentrations. As noted in Section 3, a biowaiver request for the lower strength tablets was accepted.

This study was conducted using whole tablets; however, based on *in vitro* stability studies and dose recovery data for the crushed and dissolved tablets suspended in water, the Clinical Pharmacology team agreed that an additional *in vivo* BA study was not required to support administration of crushed tablets.

Table 1 Bioequivalence Results for Proposed Product Compared to Orfadin

Nitisinone 10 mg table vs Orfadin 10 mg capsule				
PK Parameter	**Orfadin 10 mg capsule**	**Nitisinone 10 mg tablet**	**LS Mean Ratio (%)**	**90% Confidence Interval of Ratio**
$AUC_{0\text{-}120h}$ (ng*h/mL)	78149	78041	99.86	(96.34 - 103.51)
C_{max} (ng/mL)	1334	1279	95.90	(91.66 - 100.34)

Source: Table 1, Clinical Pharmacology review by S. Li, Ph.D., dated June 28, 2017

Based on results of Study CT-002, which showed no effect of a high fat, high calorie meal on the bioavailability of nitisinone tablets, the review team agreed with the proposal to label the product to be taken with or without food. Although the high fat meal resulted in a lengthening of the Tmax from three to six hours, given the long half-life of nitisinone, this is not expected to have any impact of concern. Of note, Orfadin capsules are labeled to be taken an hour before or two hours after eating, because the food effect has not been studied.

6. Clinical Microbiology

A formal review by Microbiology was not required for this oral tablet; see discussion of microbiology considerations with storage and handling of the crushed tablet formulations under Section 3.

7. Clinical/Statistical-Efficacy

This NDA did not include any efficacy studies, as it relies upon the Agency's findings of safety and efficacy for Orfadin, based upon demonstration of bioequivalence to that listed drug.

8. Safety

There were no safety findings of concern in the three studies conducted in healthy adults, as discussed in Dr. Smpokou's review. The three studies included a total of 68 subjects exposed to Orfadin and nitisinone tablets in a cross-over manner. There were no deaths or serious adverse events. Two subjects in total withdrew from the studies due to an adverse event (AE) of vomiting, both while receiving Orfadin. No AEs occurred in more than a single subject in any of the studies, and there were no AEs related to lab parameters. Common AEs across both formulations included headache, rash, nausea and vomiting.

9. Advisory Committee Meeting

The product was not a new molecular entity, and relied upon a 505(b)(2) approach referencing an approved drug. Therefore, it was determined that advisory committee consideration was not warranted.

10. Pediatrics

The Applicant had anticipated receiving Orphan Drug designation, which would have exempted the NDA from requirements of the Pediatric Research Equity Act (PREA), so they did not include an initial Pediatric Study Plan (iPSP) in the NDA submission; rather, they included a product-specific waiver request in the NDA. The Division advised the Applicant to submit a PSP during the NDA review cycle, as orphan drug designation had not been granted at the time of NDA submission and because the new dosage form triggered PREA. Subsequently, the request for orphan designation was denied.

The Applicant submitted their PSP on Dec. 16, 2016, stating:

> No additional non-clinical and clinical studies are planned by the Sponsor. By demonstrating the bioequivalence between Nitisinone Tablets and reference listed drug (ORFADIN Capsules), Cycle relies on the FDA's findings of safety and efficacy for ORFADIN capsules approved in NDA 021232 on Jan 18, 2002 and subsequent supplements, the last being June 2016.

Although the listed drug, Orfadin, was exempt from PREA due to its orphan designation, it contained a full pediatric assessment. The current Applicant notes that Orfadin has been prescribed to both adults and children, and that the phase 3 studies supporting Orfadin capsules were conducted primarily in children < 24 months of age. The current Applicant is relying on the Agency's findings of safety and efficacy, including the findings in pediatric patients, for the listed drug Orfadin.

The application was discussed at the Pediatric Review Committee (PeRC) on July 19, 2017. PeRC determined the application had fulfilled the pediatric study requirement(s) under PREA for all relevant pediatric age groups, due to its bioequivalence to the capsule formulation, provided that the tablets can be crushed and administered to the youngest patients. This has been addressed in the agreed-upon labeling (see Section 12).

11. Other Relevant Regulatory Issues

Dr. Smpokou's review includes the financial disclosure assessment.

The Office of Study Integrity and Surveillance (OSIS) recommended accepting the data from Study CT-003 without an on-site inspection, based on the recent favorable inspection of the (b) (4) Determining the extent to which the calibration range for nitisinone concentrations was representative of the study sample concentrations was deferred to the Clinical Pharmacology team (see Section 5).

OSIS provided an inspection report on the Study CT-003 site (PAREXEL in South Africa) and concluded that the data are acceptable for review. After a question was raised by the Orfadin Applicant about the current Applicant's access to Orfadin to evaluate bioequivalence, OSIS documented that the listed drug was procured and used in Study CT-003, noting that the Orfadin capsules were shipped from the manufacturer via a third-party supplier under appropriate conditions. In addition, the packaging and labeling of the capsules identified them as Orfadin, and they are visually distinct from nitisinone tablets.

There are no other unresolved relevant regulatory issues.

12. Labeling

DMEPA conditionally approved the proprietary name Nityr.

Labeling generally follows that for Orfadin, which underwent conversion to Physicians Labeling Rule (PLR) format and content in 2010 (S-008). Areas of the Nityr labeling that deviate from Orfadin's labeling are detailed in Dr. Meyer's CDTL review.

Major issues addressed in labeling included detailed dose administration instructions for patients who cannot swallow intact tablets, guidance about rounding up the weight-based dosing instructions to utilize whole tablet strengths in dosing, and inclusion of pharmacokinetic and food effect information from Studies CT-002 and CT-003. The Patient Labeling Team and pediatric reviewer from DPMH provided substantial revisions to the Prescribing Information and Instructions for Use (IFU) to ensure clear information about preparing the crushed or disintegrated tablets for administration and to mitigate any risk of choking due to administration of incompletely crushed or dissolved tablets. In particular, labeling clearly states that administration of Nityr with other liquids or foods (aside from water and applesauce) is not recommended, and that the suspension should not be administered if the tablet has not fully disintegrated. The maternal health reviewer from DPMH reviewed the labeling with respect to the Pregnancy and Lactation Labeling Rule (PLLR) and concluded that there are no new data relevant to this section since the last DPMH review regarding nitisinone, and that the PLLR labeling will remain consistent with that for Orfadin.

Carton and container labeling was found acceptable by DMEPA and OPQ. Final agreement with the Applicant on labeling was reached on July 25, 2017, and recommendations by the primary and consulting review disciplines, including DPMH, DMEPA, DMPP and OPDP, have been incorporated into the labeling.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

I agree with the recommendation of the CDTL, Joette Meyer, Pharm.D., that Nityr tablets be approved for the treatment of hereditary tyrosinemia type 1 in combination with dietary restriction of tyrosine and phenylalanine.

- **Risk Benefit Assessment**

The data submitted in this 505(b)(2) NDA do not change the benefit/risk assessment of nitisinone in general, and do not raise any additional risks specific to the tablet formulation (or the administration of crushed tablets in semi-solid food or water) relative to the already approved capsule formulation. The benefit/risk analysis remains favorable for oral nitisinone.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

None are needed beyond labeling.

- **Recommendation for other Postmarketing Requirements and Commitments**

The Applicant has agreed to a post-marketing commitment to conduct and report the results of assays of the two pediatric preparations (crushed tablets mixed with applesauce and an aqueous solution of disintegrated tablets in water) at room temperature to ensure that the proposed storage and handling periods do not compromise the strength of the drug administered. The study is currently underway; agreed-upon milestones are:

- Study/Trial Completion: 9/19/2017
- Final Report Submission: 9/26/2017

The Applicant also plans [redacted] (b) (4)

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/s/

LISA M SOULE
07/26/2017